EBMT European Society for Blood and Marrow Transplantation

Infections after stem cell transplantation

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No conflict of interest

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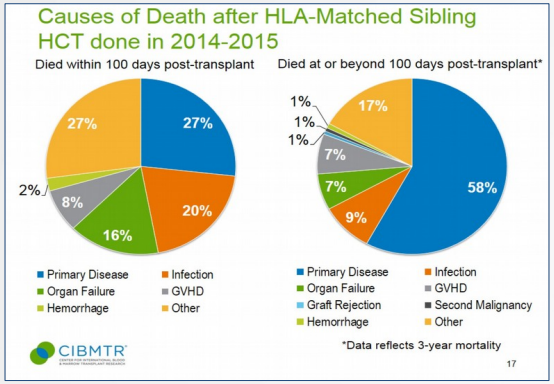
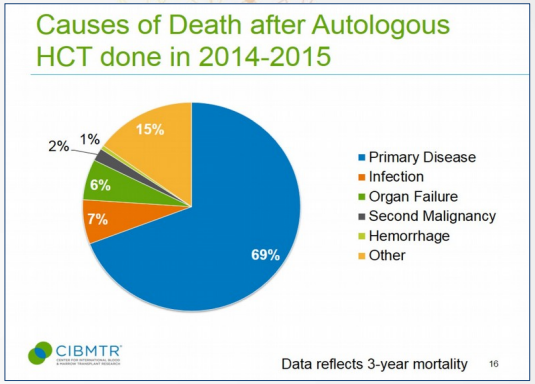
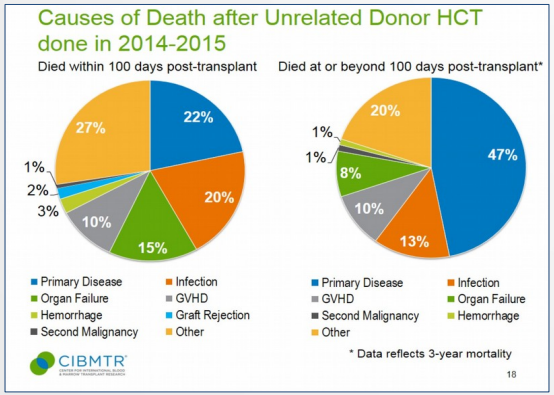
Infections after HSCT

- **Infectious complications – universal problem**
  - Hematological malignancies - impaired immune system
  - HSCT - immune-directed treatment
  - Common pathomechanism of selected infections and hematological malignancies
  - Characteristics
    - Opportunistic infections
    - Atypical symptoms and rapid dissemination of infection
    - Delayed diagnosis – increased mortality

Mortality after HSCT







Early mortality from infections

autoHSCT 7%
alloHSCT sibling
20% alloHSCT UD
20%

Mortality after HSCT

SPAIN

ECOG performance
Age >60 years
aGVHD≥2
Invasive fungal infection
CMV infection

Martino et al. BMT 2011

SWEDEN

aGVHD≥2
extensive cGVHD
CMV infection
MMUD
TBI

Bjorklund et al. BMT 2007

AUSTRALIA

Organ insufficiency
Invasive fungal infection
CMV reactivation

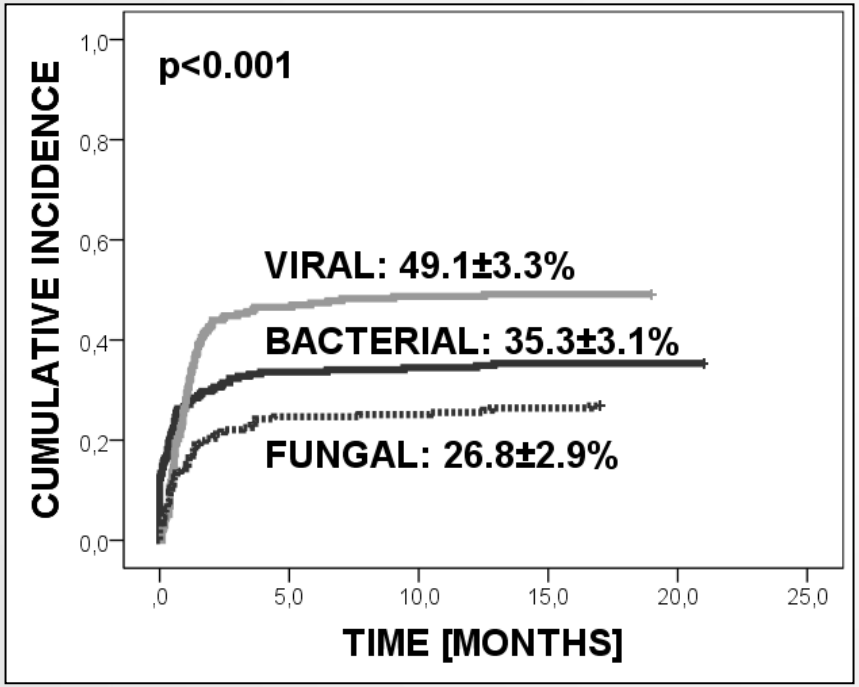
Agarwal i wsp, Intern Med. J, 2012

TAIWAN

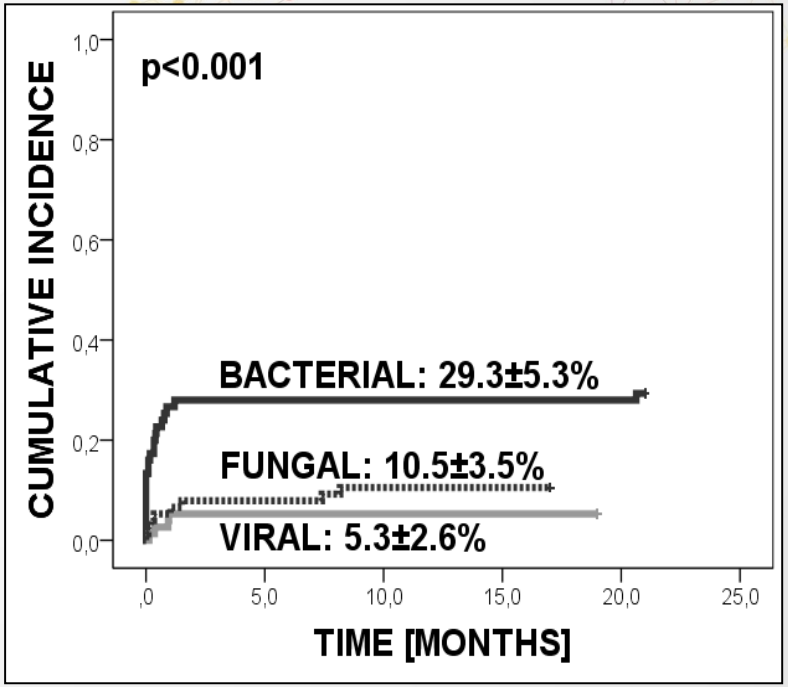
Pneumonia (bacterial)
Pneumonia (CMV)
Invasive fungal infection
Sepsis

Yang i wsp, J Formos Med. Assoc, 2007

Incidence of infections

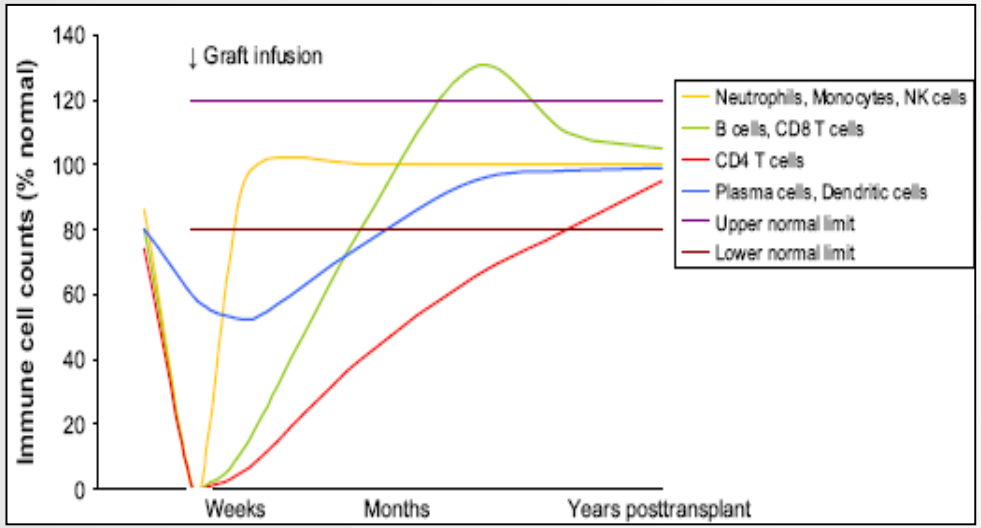


alloHSCT



autoHSCT

Immune reconstitution after HSCT



Risk factors

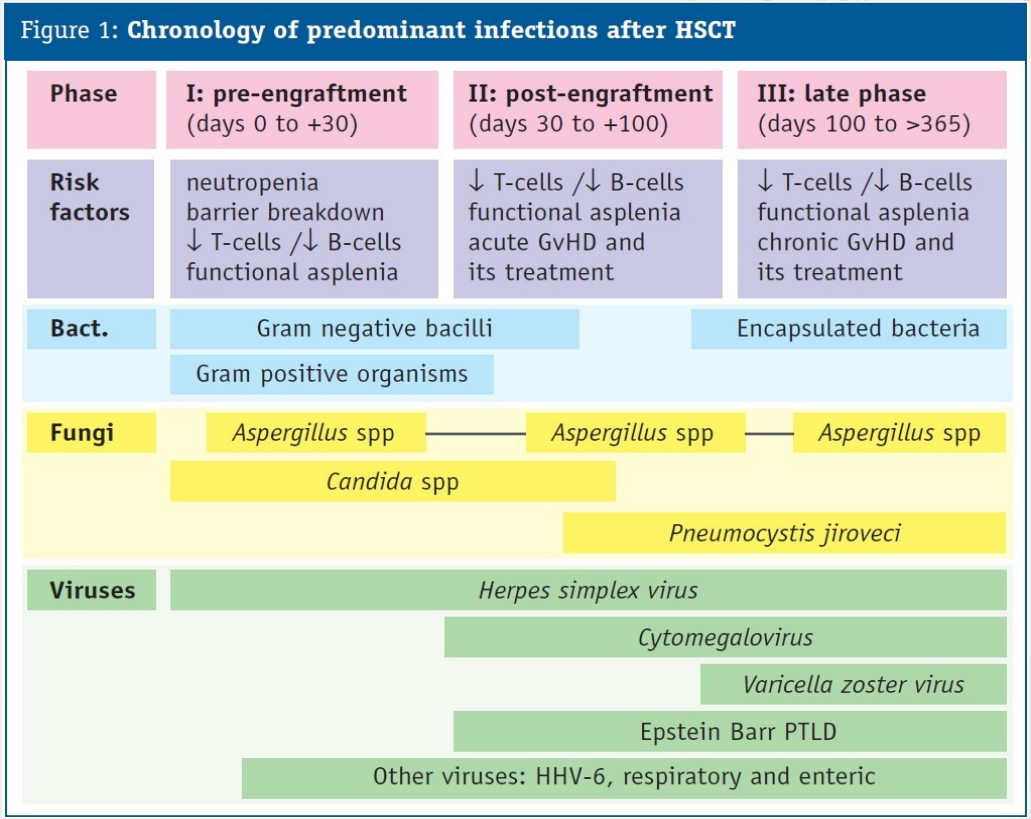
- type of transplantation
  - auto vs allo
- source of stem cells
  - PB vs BM vs CB
- conditioning regimen
  - RIC vs MAC
- degree of histocompatibility
- GVHD prophylaxis
- GVHD occurrence and grade

Status of hematological disease at HSCT
Co-morbidities
Neutropenia – degree and lenght
Disruption of anatomical bariers
Depressed T and B cell function

Storek et al. Expert Opinion 2008

Infections after HSCT

Figure 1: **Chronology of predominant infections after HSCT**



Adapted from (2). PTLD: post-transplant lymphoproliferative disorder

Infections after HSCT

Strategies	Etiology
Definition Risk group Diagnosis and monitoring Prophylaxis Treatment Empirical Preemptive Targeted	Bacterial Fungal Viral Protozoal

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Bacterial infections

Neutropenia: pre-engraftment phase

Risk factors for infections

- Neutropenia length >7 days
- Severe neutropenia < 0.5 G/L
- Mucositis
- Central venous catheters
- Immunologic impairment

Infections during neutropenia

- Febrile of unknown origin (FUO)
- Clinicaly documented infections
- Microbiologically documented infections

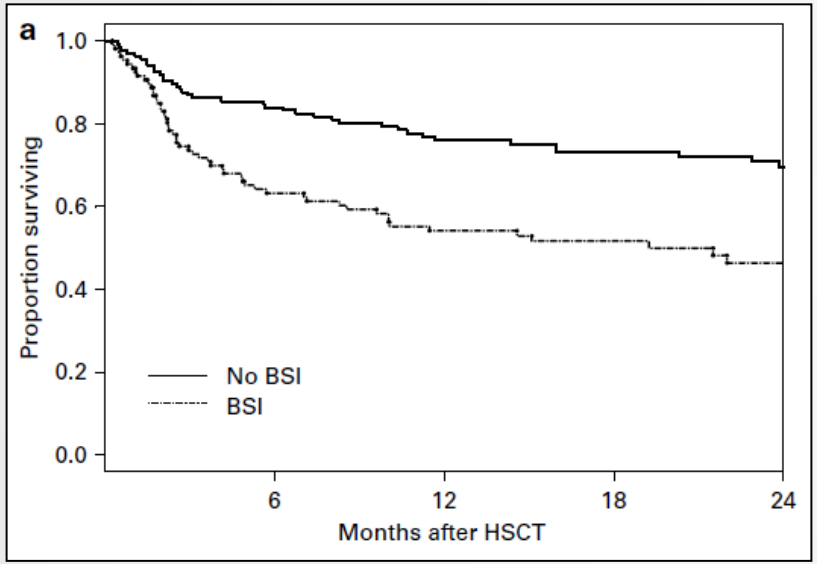
Neutropenic fever

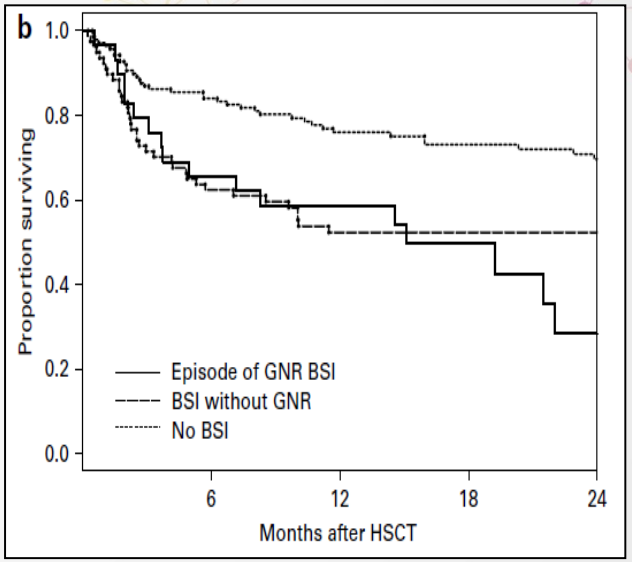
- **Infections during neutropenia: 35-89%**
- **Bloodstream infections: 20-60%**
- **Gram positive bacteria >50%**
  - *Staphylococcus sp., Enterococcus sp., Streptococcus viridans*
  - ***VRE, MRSA, MRSE***
- **Gram negative bacteria**
  - **Increased rate**
  - **Mortality: 24-50%**
  - ***P. aeruginosa, E. coli, Klebsiella pneumoniae, Acinetobacter baumani, Enterobacter cloacae, Stenotrophomonas maltofilia***

Neutropenic fever – treatment strategy

- **Prophylaxis**
  - Enviromental
  - Pharmacological
- **Empirical antibiotic therapy**
  - De-escalation
  - Escalation
- **Targeted therapy**
  - Antibiotic choice
  - Treatment duration
  - Antibiotic dose

Bacterial infections





Mortality associated with bloodstream infection after HSCT

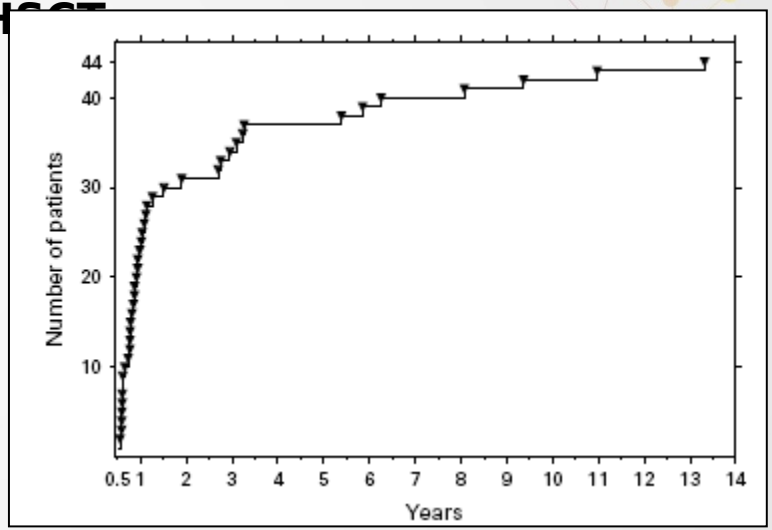
Risk factors for BSI: alloSCT and degree of HLA matching

Pre-engraftment phase

Important data	
Neutropenia at time of infection onset Lengh of neutropenia Severity of neutropenia Etiology of bacterial infection Gram positive bacteria Gram negative bacteria	Site of infection Bloodstream infection Pneumonia Central nervous infection Abdominal infection Urinary tract infection Skin infection Prophylaxis Treatment Empirical Targeted Outcome

Post-engraftment and late infections

- **Late infection > 6 months after HSCT**
  - 6,4% deaths
  - 66% infection – about 18 month
- **Characteristic**
  - Pneumonia
  - Septic shock
  - Neuroinfection
- **Risk factors for mortality**
  - GVHD
  - MUD, MMUD
  - CMV
  - TBI



Ljungman et al. BMT 2007

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Fungal infections

Invasive fungal disease

1213 autopsies: 371 (31%) IFI

No of autopsies 0,63 vs 0,06

Antemortem: **16% vs 51%**

AML/MDS: 31% vs 55%

alloHSCT : 30% vs 47%

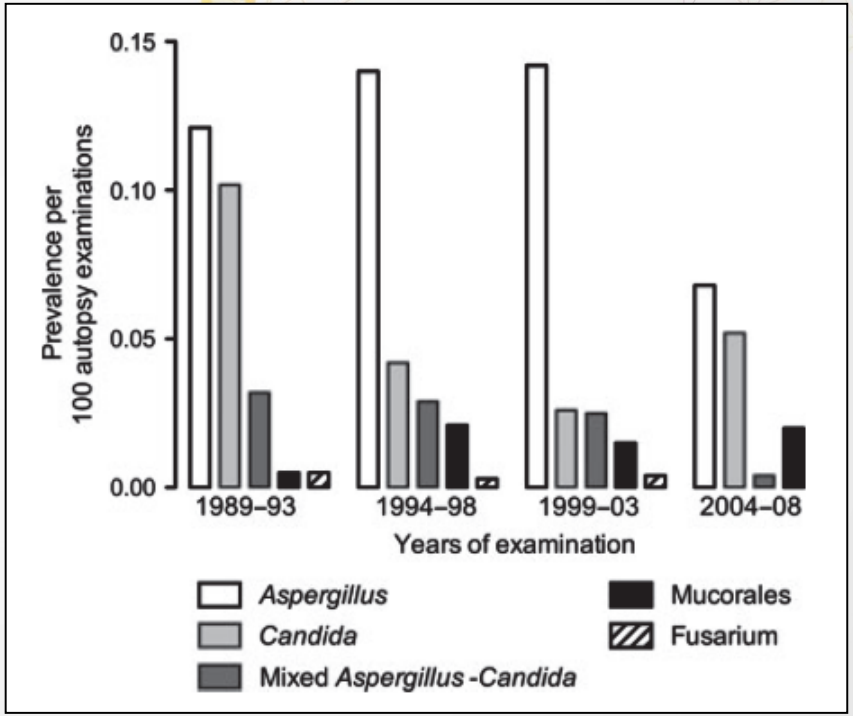
Risk factors

neutropenia: 90% vs 44%

steroid therapy: 21% vs 81%

GVHD: 16% vs 37%

Mortality 80% vs 49%

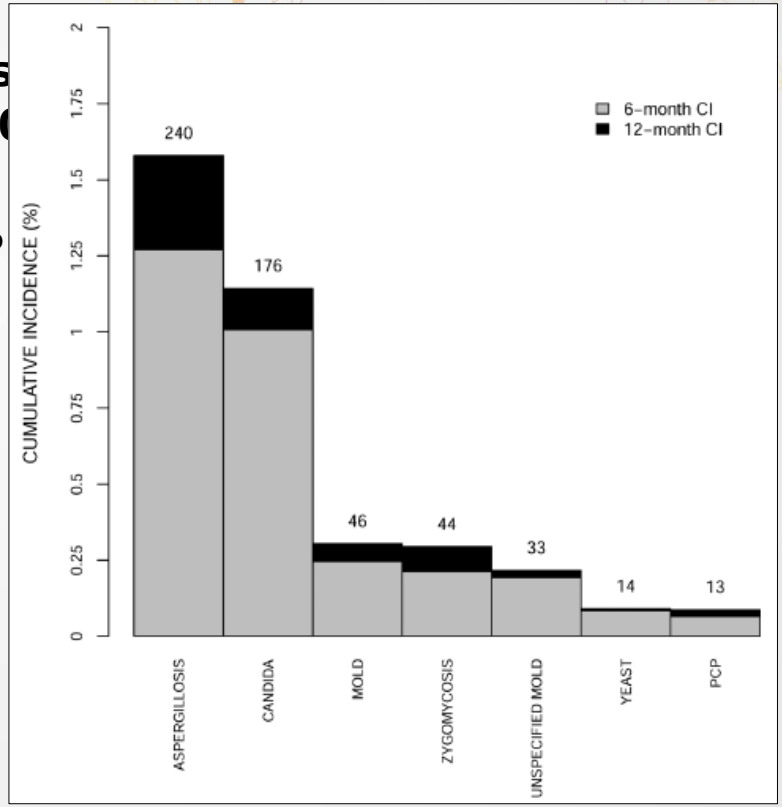


Autopsy study 1989-2008. Lewis et al. Mycoses 2013

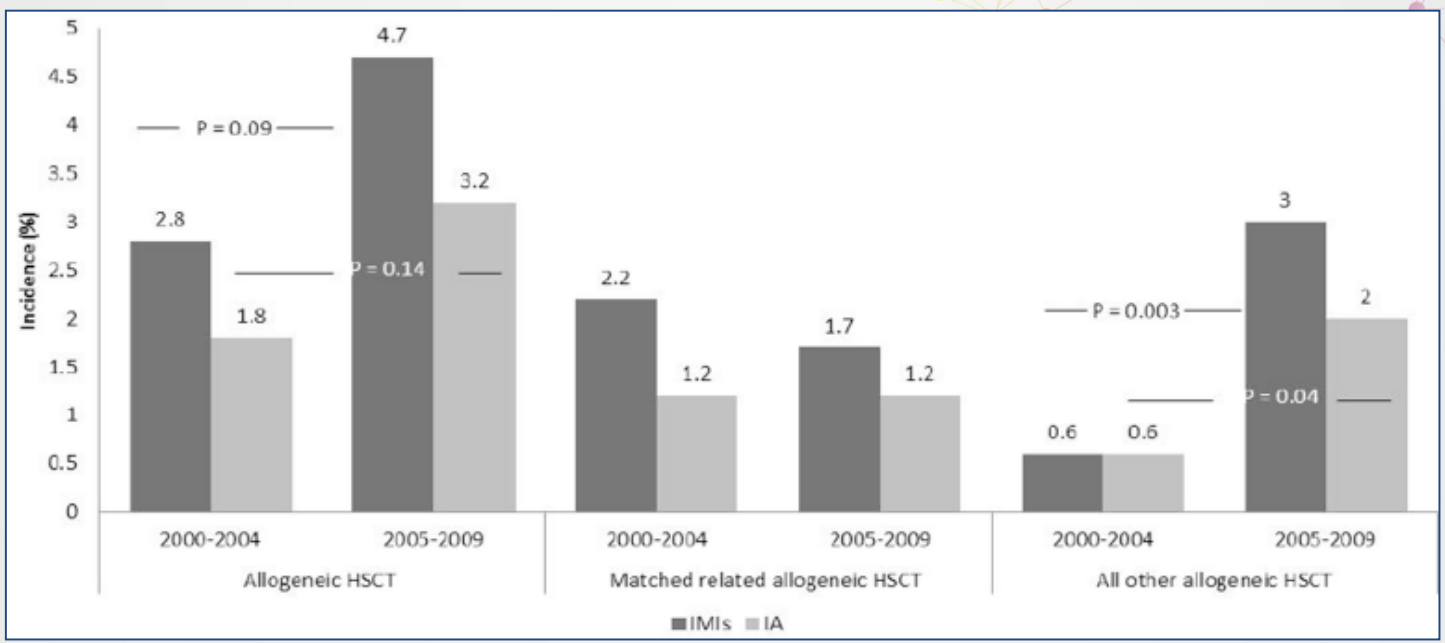
Invasive fungal disease

Prospective analysis - 15820 patients
HSCT (6286 allo; 9534 auto) 2001-20(

- **Invasive fungal disease 0,9-13,2%**
  - alloHSCT 5,8-13,2%
  - autoHSCT 0,9-1,2%
- **Invasive candidiasis 28%**
  - 61 days after HSCT
  - Mortality 64,4%
- **Invasive aspergillosis 43%**
  - 99 days after HSCT
  - Mortality 74,6%

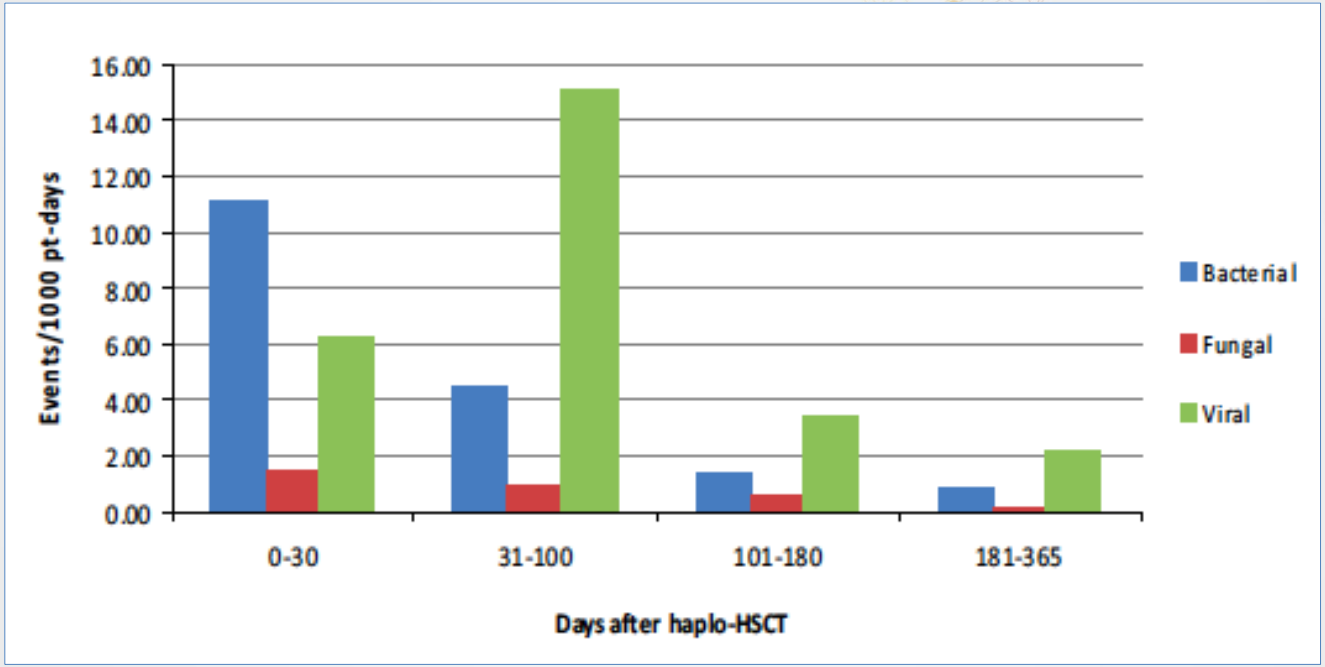


Invasive fungal disease



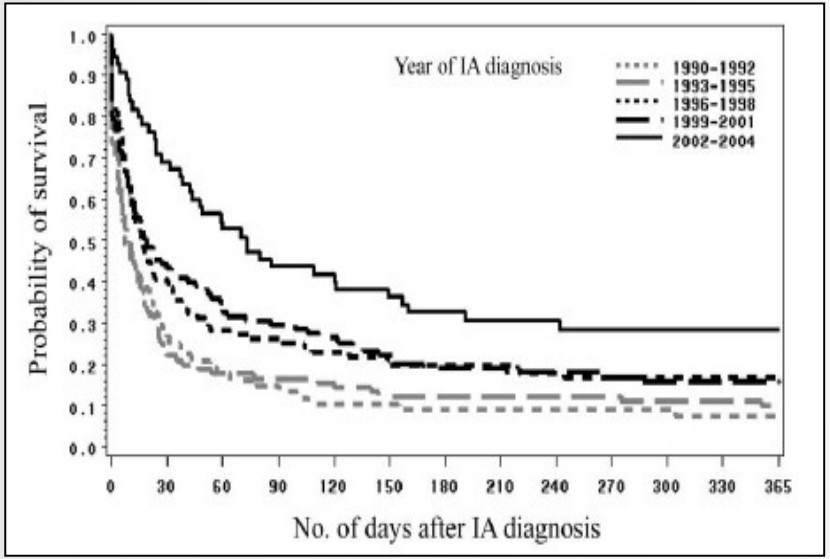
Invasive fungal disease after alloSCT

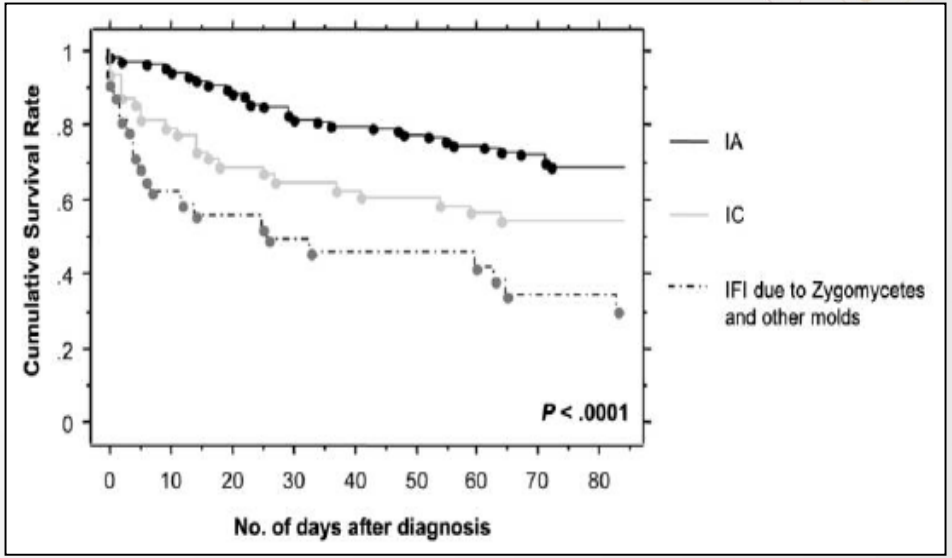
Infections after haploHSCT-PCy



Infections at different post-transplant intervals

Invasive fungal disease





405 pts; Upton et al. CID 2007

234 pts; Neofytos et al. CID 2009

Invasive fungal disease

Figure 3: **Main criteria for proven, probable and possible invasive fungal infection**

Proven IFI	Probable IF	Possible IFI
Histological or culture evidence (in sterile material)	Host factors (neutropenia, immunosuppressants) + **Mycological criteria** (direct - cytology, culture of non sterile material - or indirect tests - GM or βDG) + Clinical criteria (+CT/MRI, FBS, retinal)	Host factors + **Clinical criteria**

GM: galactomannan; βDG: beta-D-glucan; FBS: fibrobronchoscopy. Retinal: retinal images suggestive of IFI. For complete description of host, clinical and microbiological criteria see reference (22)

Prophylaxis – risk group

- primary
- secondary

Antifungal therapy

- empirical
- preemptive
- targeted

Invasive fungal disease

Important data

- IFD in the history
- Condition at time of infection onset
  - Neutropenia
  - GVHD
- Level of diagnosis
- Etiology
  - Mold infections
  - Candida infections
- Site of infection
  - Lung
  - Boodstream infection
  - Central nervous system infection
- Prophylaxis
- Treatment
  - Empirical
  - Preemptive
  - Targeted
- Outcome

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Viral infections

Viral infections after HSCT

Latent infections		Sporadic infections	
virus	% seropositive patients	virus	% infections
HSV 1/2	50-90%	RSV	5-15%
VZV	>90%	Parainfuenza	5-10%
CMV	45-90%	Influenza	<5%
HHV-6	>90%	Adenovirus	<5%
EBV	>90%	Rhinovirus	<5%
BKV	>90%	Metapneumovirus	5-20%

CMV infections and disease

- CMV infection remains amongst **the most common** and significant complications after HSCT
- Cumulative incidence of CMV reactivation among alloHSCT is around **36%** and in CBT recipients could be as high as **80%**
- CMV end-organ disease: CMV pneumonia ranges from **10% to 30%** in alloSCT recipients
- CMV disease is **costly** and is associated with **prolonged hospital stay**

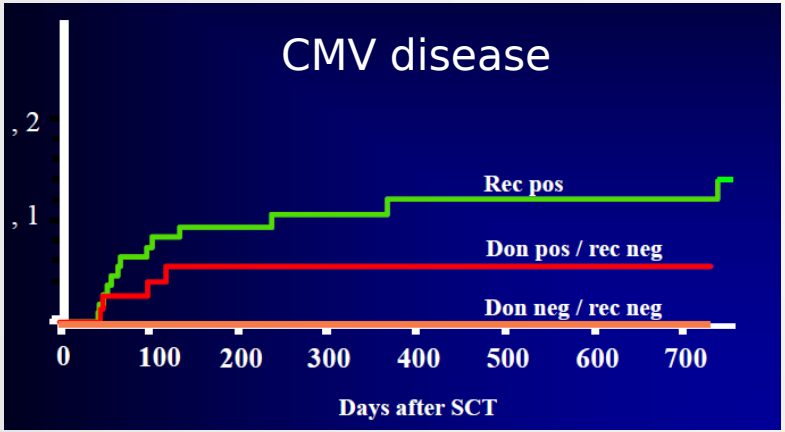
Direct effects	Indirect effects	Drug toxicity
• Breakthrought CMV disease (patients on prophylaxis or PET) • Late CMV disease • Resistant CMV disease	• Bacterial infection • Fungal infection • GVHD	• Myelosuppression • Renal failure

CMV management

- **Diagnostic procedures**
  - D/R serology before HSCT
  - CMV monitoring post HSCT
    - CMV-DNA (quantitative, qualitative)
    - CMV-mRNA
    - Antigen pp65
- **Prevention of primary CMV infection**
  - Donor selection
  - Blood product transfusion: CMV(-)
- **Prevention of CMV disease**
  - Donor selection
  - Prophylaxis
  - Preemtive treatment (PET)
- **Treatment of CMV disease**

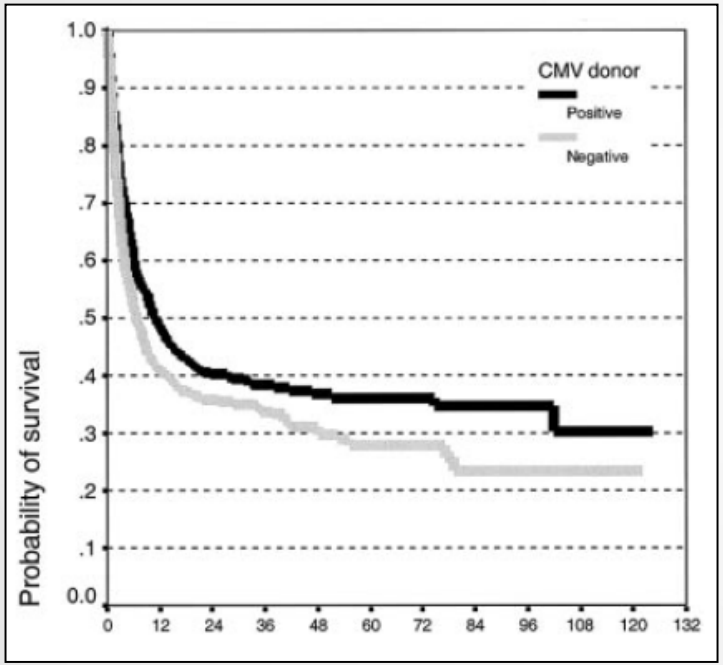
CMV reactivation and disease

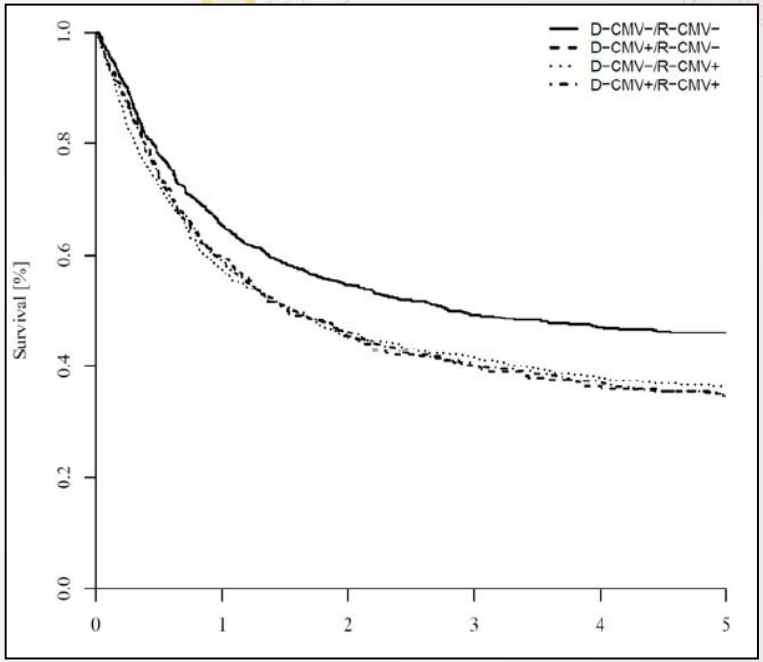
	RISK OF CMV REACTIVATION	OVERALL SURVIVAL
R- / D-	0%	BETTER THAN IN R-/D+
R- / D+	30%	
R+ / D-	80%	
R+ / D+		BETTER THAN IN R+/D-



- CMV-seropositive donor for a CMV-seronegative patient is associated with decreased survival
- CMV-seronegative unrelated donor for a CMV-seropositive patient is associated with decreased survival
- Serology before transplant determines the risk of the disease after transplant

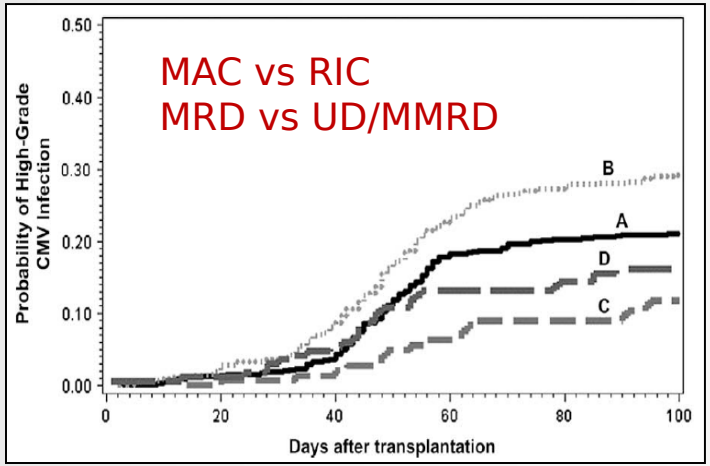
CMV – impact on survival

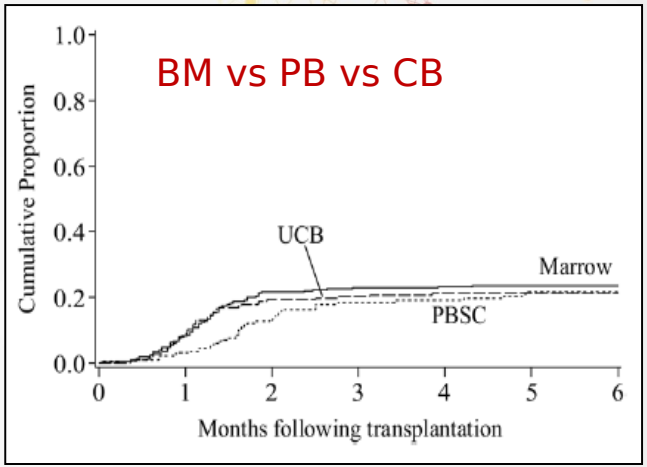




Decreased survival in CMV seropositive patients

CMV reactivation





Cumulative incidences of CMV infection in CMV HR pts:

(A) Myeloablative MRD,
(B) Myeloablative unrelated/MMRD
(C) Nonmyeloablative MRD
(D) Nonmyeloablative unrelated/MMRD

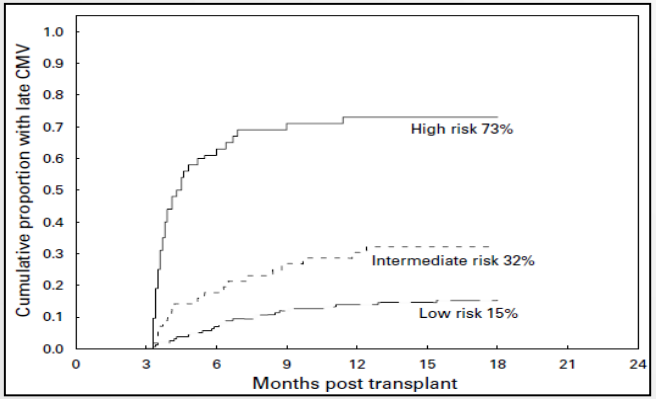
Factor	RR (95% CI)	P
CMV serology		
R−/D−	1.0	
R−/D+	1.9 (0.8-4.6)	.14
R+/D−	14.5 (8.3-25.5)	<.01
R+/D+	12.0 (6.5-22.4)	<.01
GVHD prophylaxis		
No T cell depletion	1.0	
T depletion	2.2 (1.2-3.2)	<.01
Acute GVHD (time dependent)		
No	1.0	
Yes	2.5 (1.8-3.5)	<.01
Graft source		
Marrow	1.0	
UCB	0.8 (0.5-1.3)	.44
PBSC	0.6 (0.4-1.0)	.06
Age		
<18 years	1.0	
≥18 years	1.4 (1.0-2.0)	.05

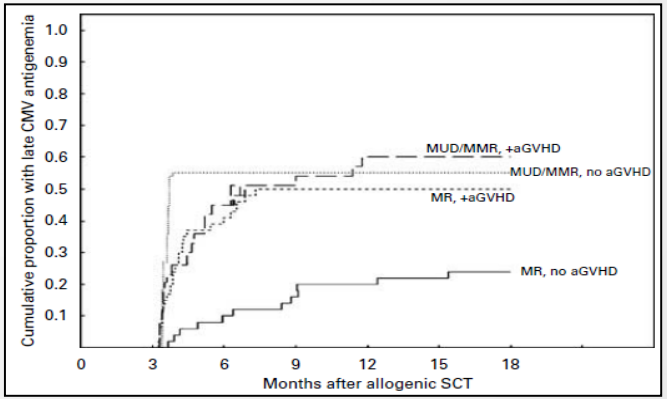
Nakamae et al. BBMT 2013

Walker et al. BBMT 2007

Late CMV infection

Risk classification	*Clinical factors*	*CI (%)*	*HR*	P-*value*
Low	Patients with no antecedent early reactivation	15	Ref.	
	MR, no aGVHD and myeloid	15	0.97	0.96
Intermediate	MUD/MMR/MR + aGVHD and myeloid/ ⩽2 early reactivation episodes	25	1.5	0.4
	MUD/MMR/MR + aGVHD and >2 early reactivation episodes/*LC>900/P+D+	42	3.0	0.02
	MR, no aGVHD and Lymphoid	39	2.6	0.03
High	MUD/MMR/MR + aGVHD and >2 early reactivation episodes, *and*			
	No lymphopenia at day 100/P+D−	83	11	<0.001
	Lymphopenia at day 100/P+D−	81	19	<0.001
	Lymphopenia at day 100/P+D+	65	9	<0.001

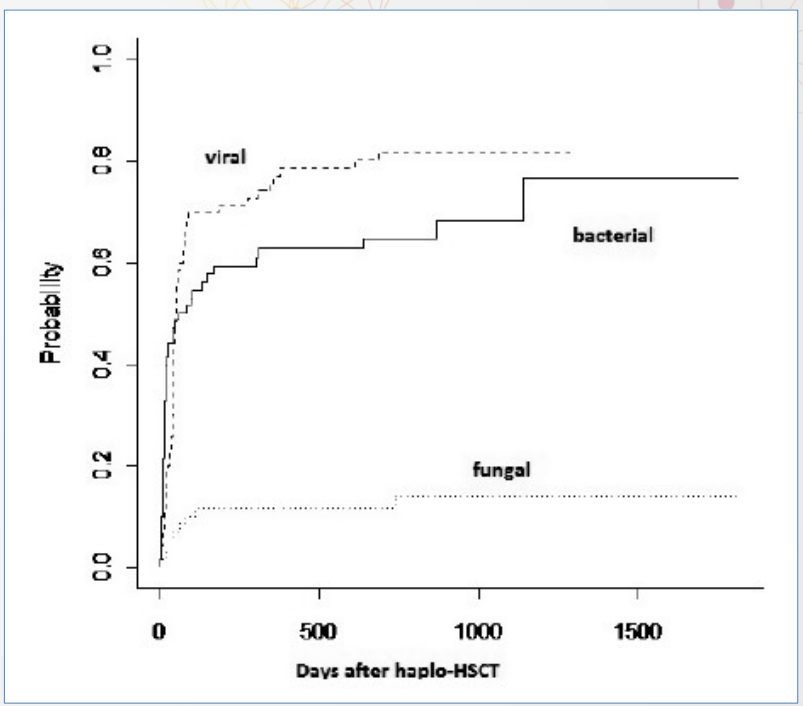




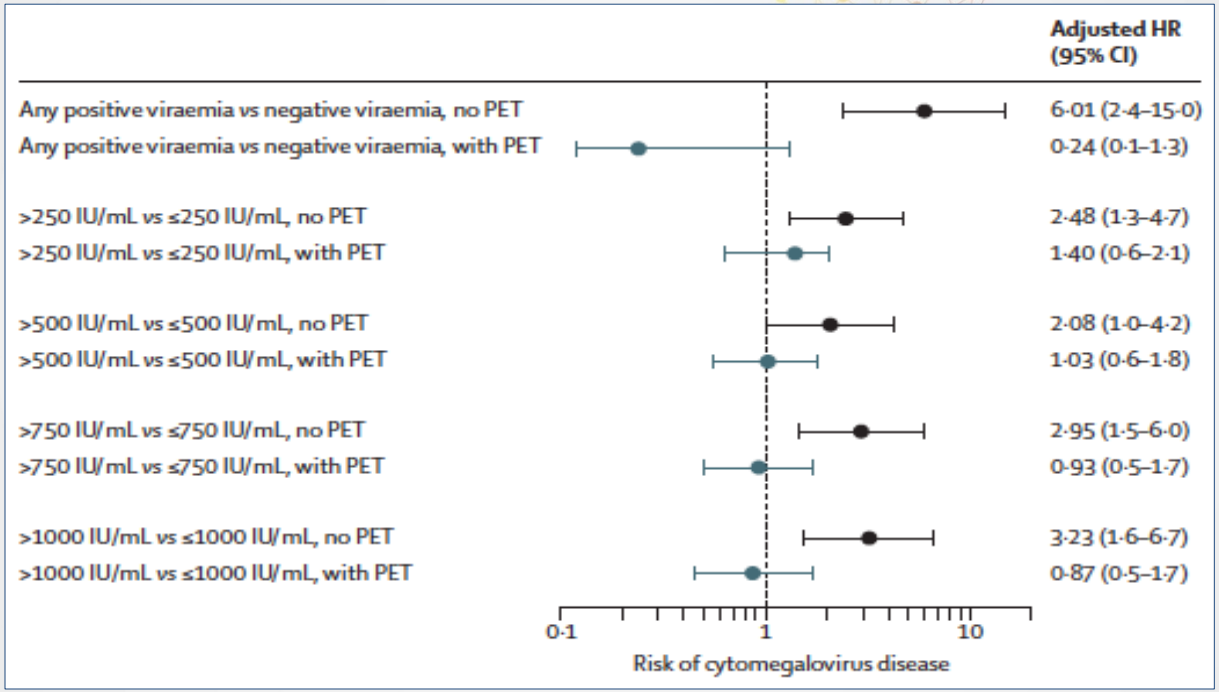
Viral infections after haploHSCT-PTCy

Patients: 70 haploHSCT-PTCy
Engraftment: 91%
aGVHD (2-4) 23%
aGVHD (3-4) 4%
chGVHD 8%
Relapse 26%
TRM 26%
2-y OS 48%
Infections
- CMV 54%
- bacterial 40%
- fungal 5%

Infection-rel deaths 9%



Viral load and CMV disease

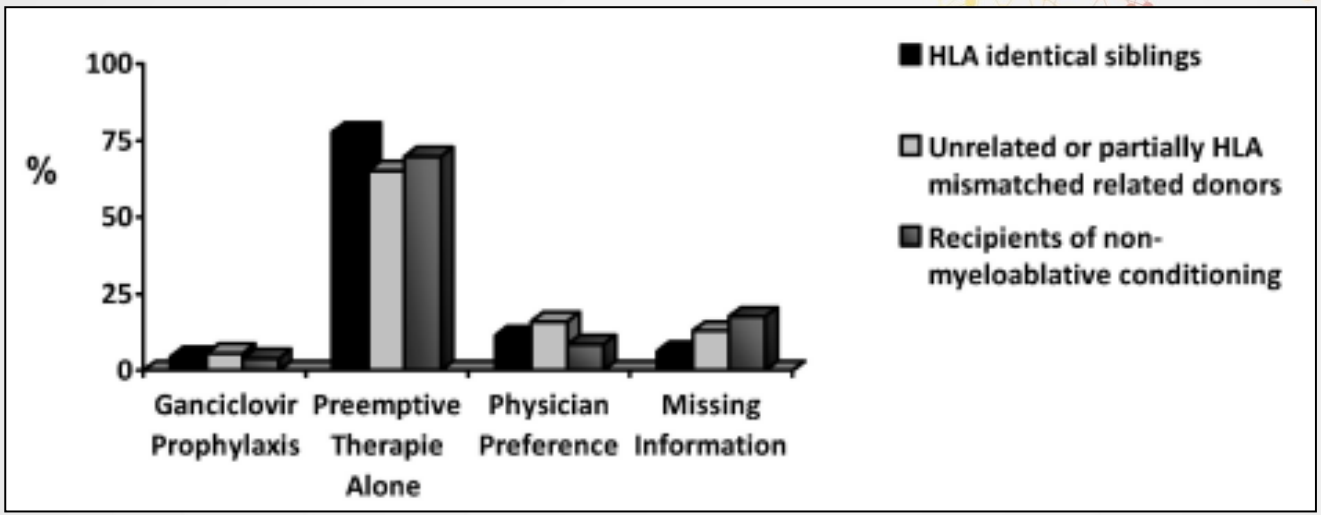


Model assessing CMV viral load as a time dependent risk factor for CMV disease 1 year after HSCT stratified by use of pre-emptive therapy

Viral load and CMV disease

- **CMV viral load is associated with increased risk of CMV disease**
- **The risk is attenuated by use of pre-emptive antiviral therapy**
- **Increased viral load thresholds are associated with**
  - **CMV disease**
  - **Bacterial and fungal infections**
  - **An increased risk of death without relapse**
  - **But not GVHD**

CMV reactivation



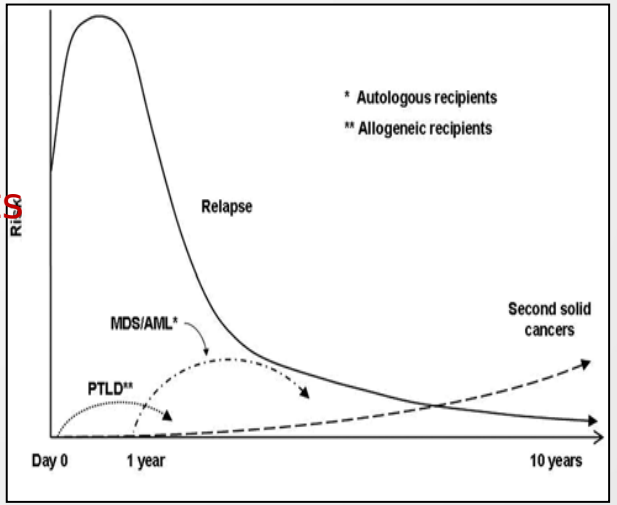
Prophylaxis	Pre-emptive treatment	Therapy
Ganciclovir	Ganciclovir	Ganciclovir
Aciclovir	Valganciclovir	Foscarnet
Valaciclovir	Foscarnet	Cidofovir
Foscarnet	Cidofovir	CMV-CTL
Letermovir		

Pollack et al. BBMT 2012 Ljungman et al. BMT 2008

Epstein-Barr Virus

- EBV infection occurs in over 80-90% of world's population
- First human virus implicated in oncogenesis
- Remain latent in B-cells
- After primary lytic infection, EBV maintains a steady low grade latent infection in the body
- During periods of immunosuppression, the virus may reactivate to cause clinical disease

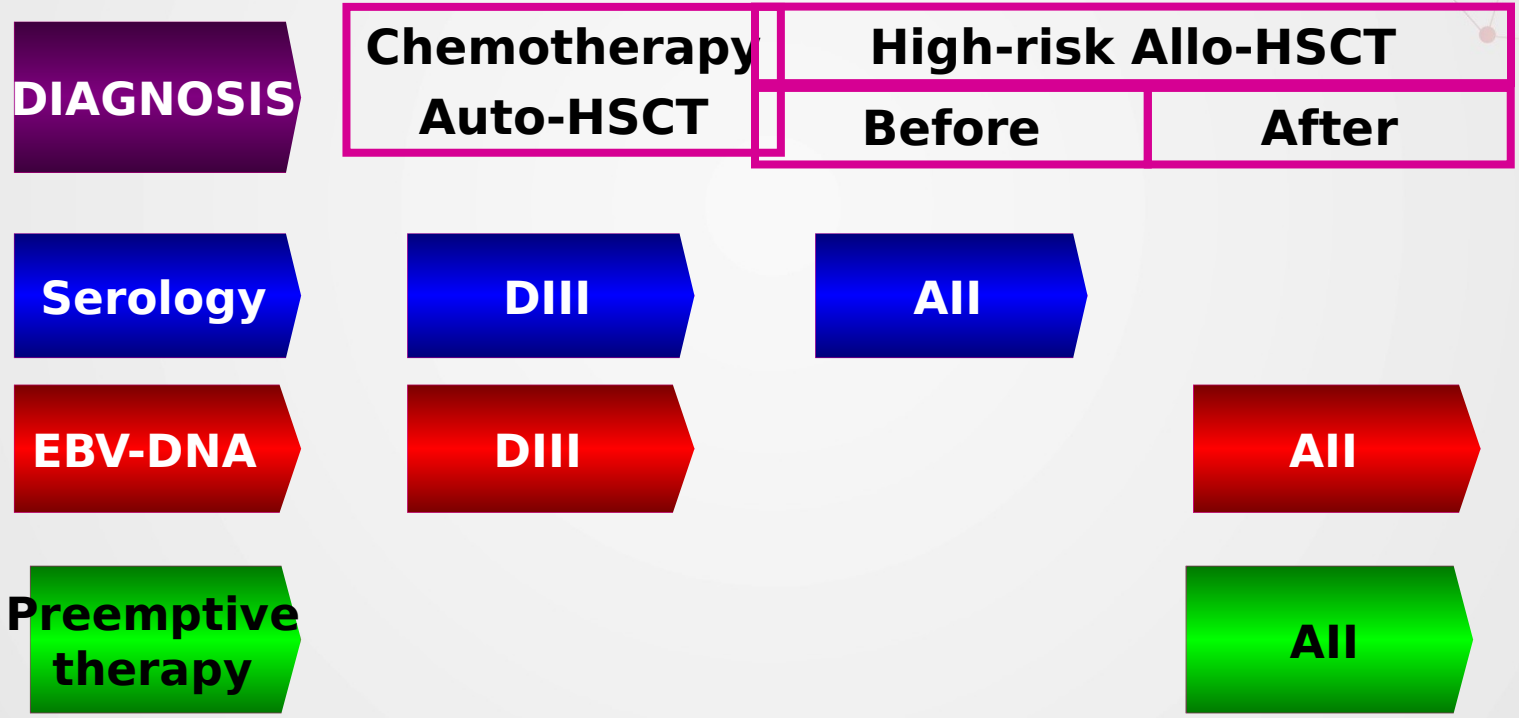
- Important complication in HSCT patients
- EBV-driven B-cell proliferation: „second malignancy" EBV-PTLD



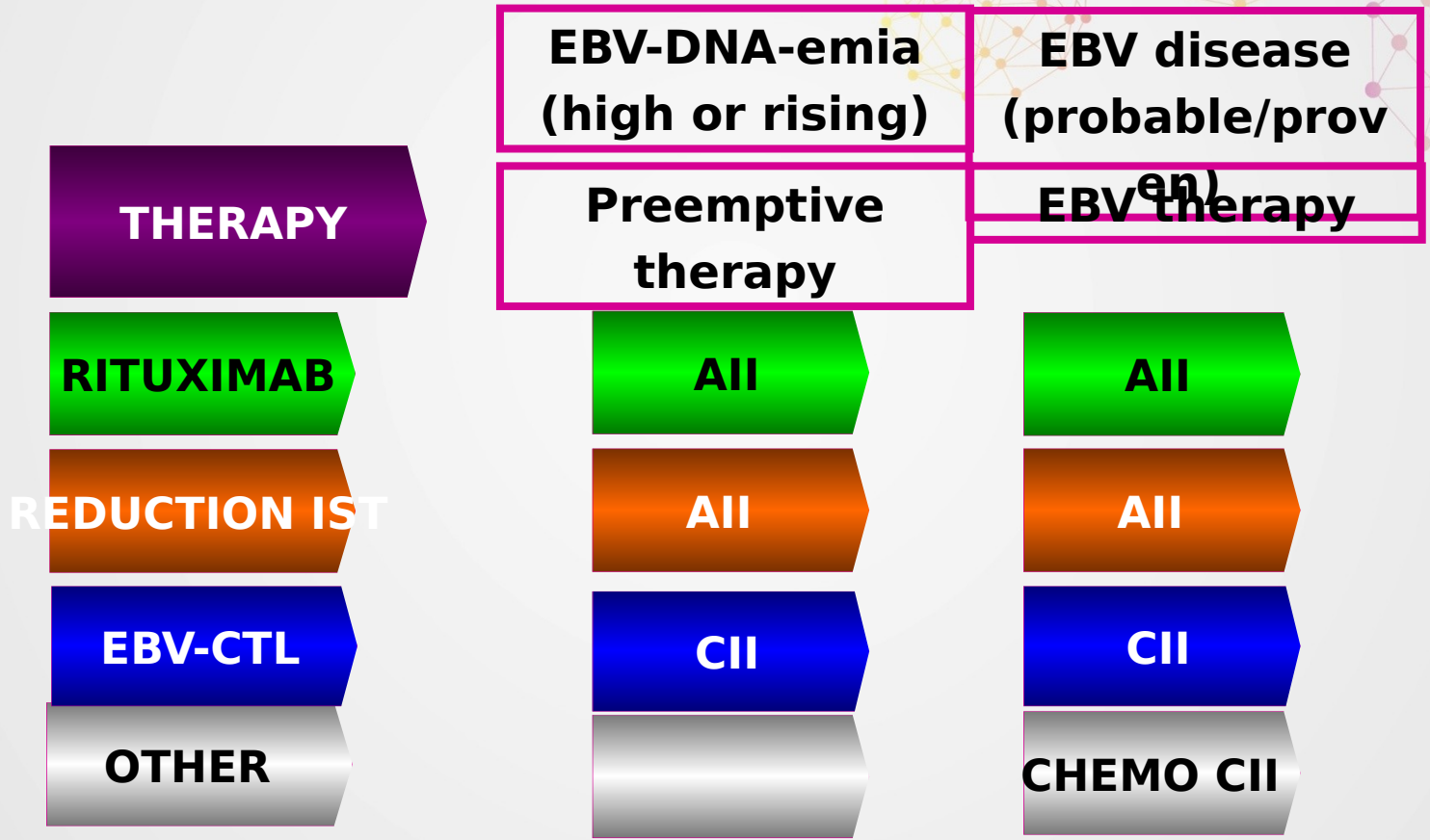
EBV infection - definition

- **Primary EBV infection - EBV detected (nucleic acid or serologically) in a previously EBV-naive patient**
- **EBV-DNA-emia - Detection of EBV DNA in the blood**
- **Proven EBV disease - confirmed by biopsy**
- **Probable EBV disease - clinical symptoms with high EBV blood load (without biopsy)**
- **Post-Transplant Lymphoproliferative Disorder (PTLD) - Heterogenous group of EBV diseases with neoplastic lymphoproliferation, developing after transplantation and caused by iatrogenic suppression of T-cell function**

Management of EBV infection

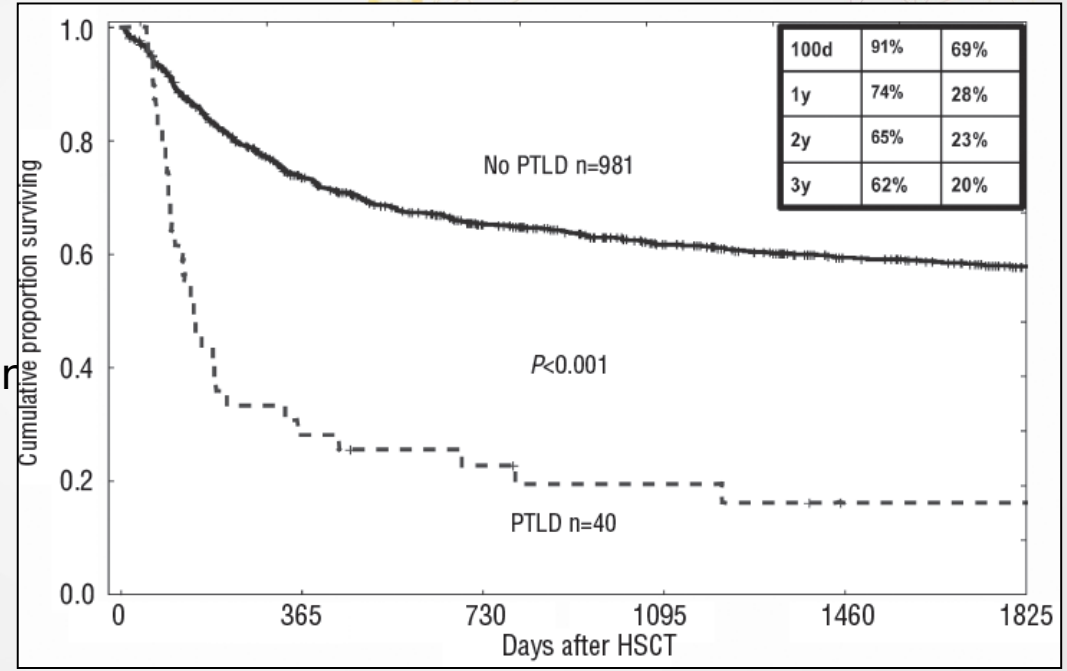


Therapy of EBV infection



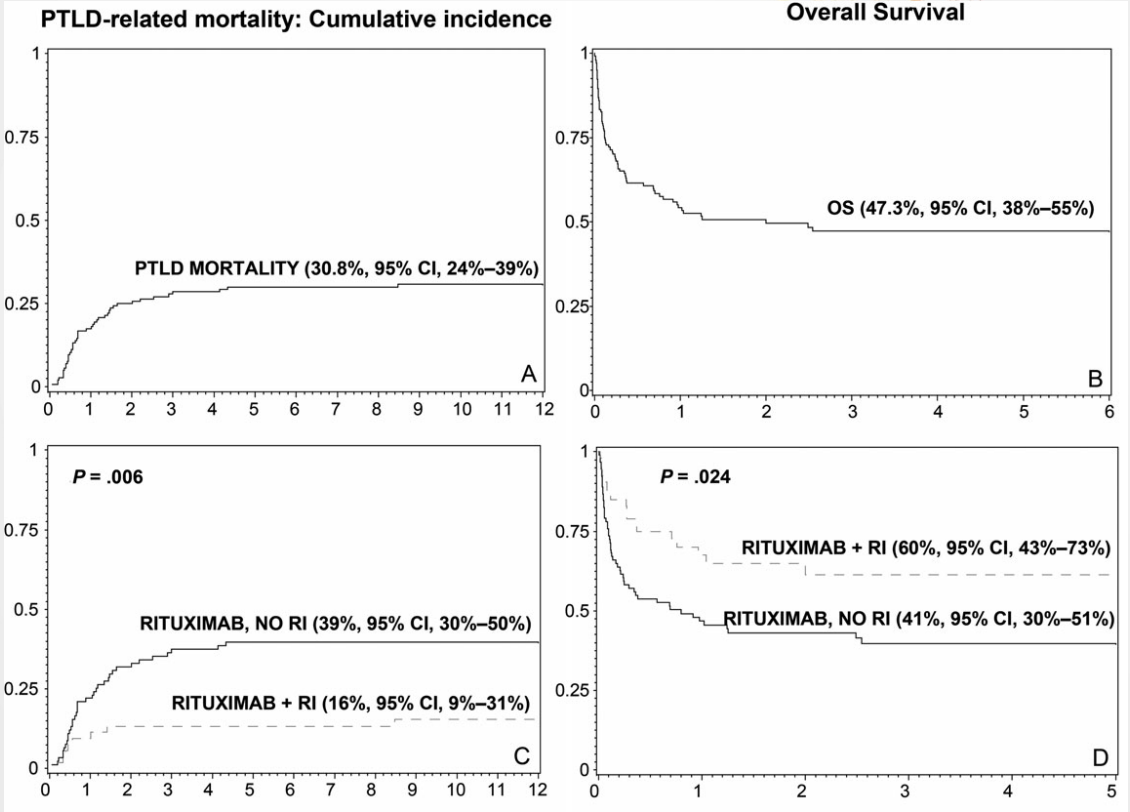
EBV-PTLD

- Increasing incidence
- PTLD develops usually within first year after HSCT
- Delayed diagnosis and treatmer – increased mortality

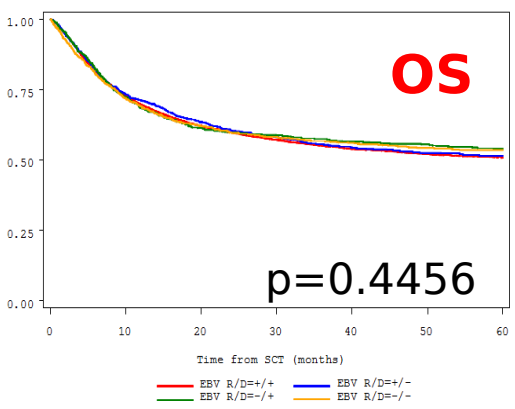


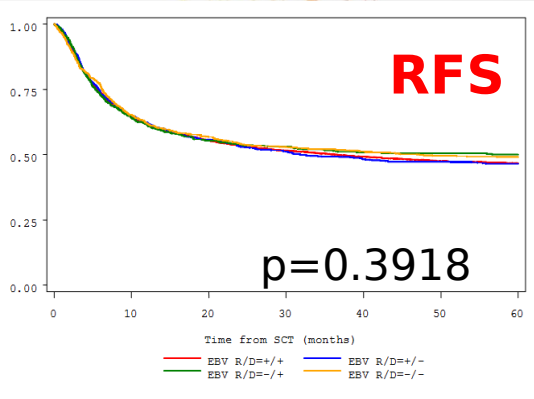
PTLD – mortality after alloHSCT. Uhlin et al. Haematologica 2014

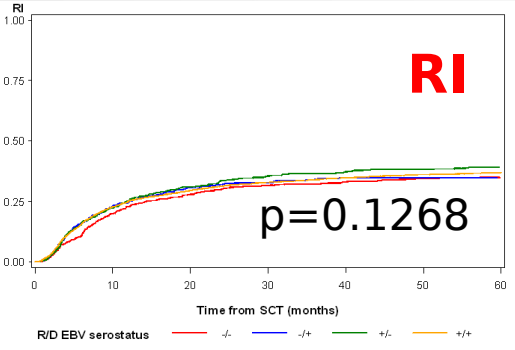
EBV-PTLD

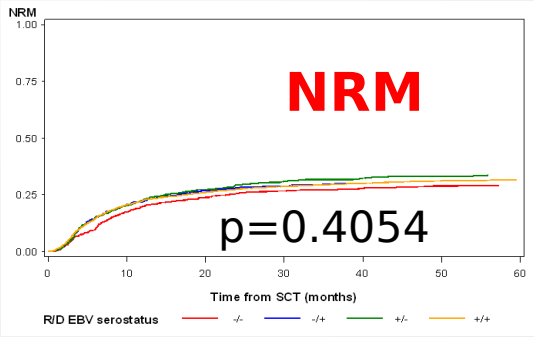

PTLD-related mortality: Cumulative incidence
PTLD MORTALITY (30.8%, 95% CI, 24%–39%)
A
Overall Survival
OS (47.3%, 95% CI, 38%–55%)
B
P = .006
RITUXIMAB, NO RI (39%, 95% CI, 30%–50%)
RITUXIMAB + RI (16%, 95% CI, 9%–31%)
C
P = .024
RITUXIMAB + RI (60%, 95% CI, 43%–73%)
RITUXIMAB, NO RI (41%, 95% CI, 30%–51%)
D

EBV serostatus – transplant outcome

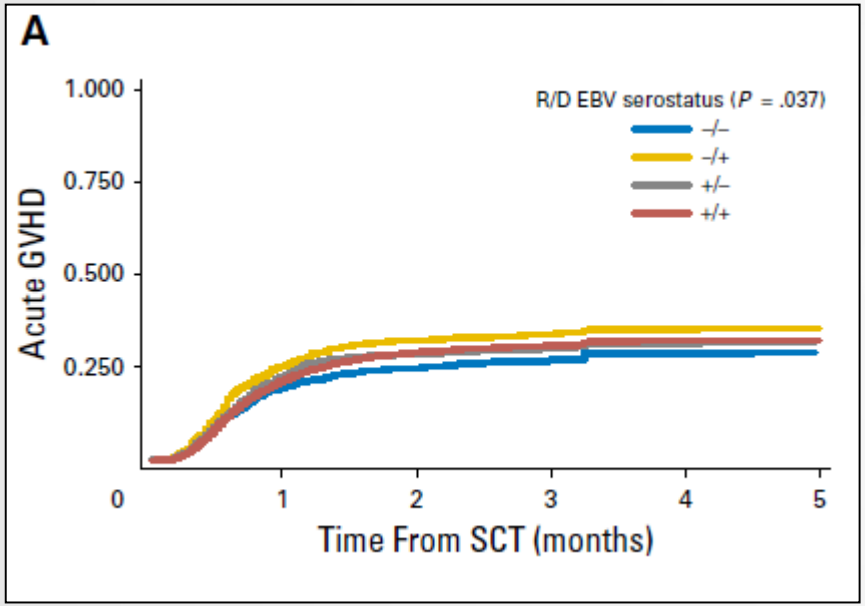


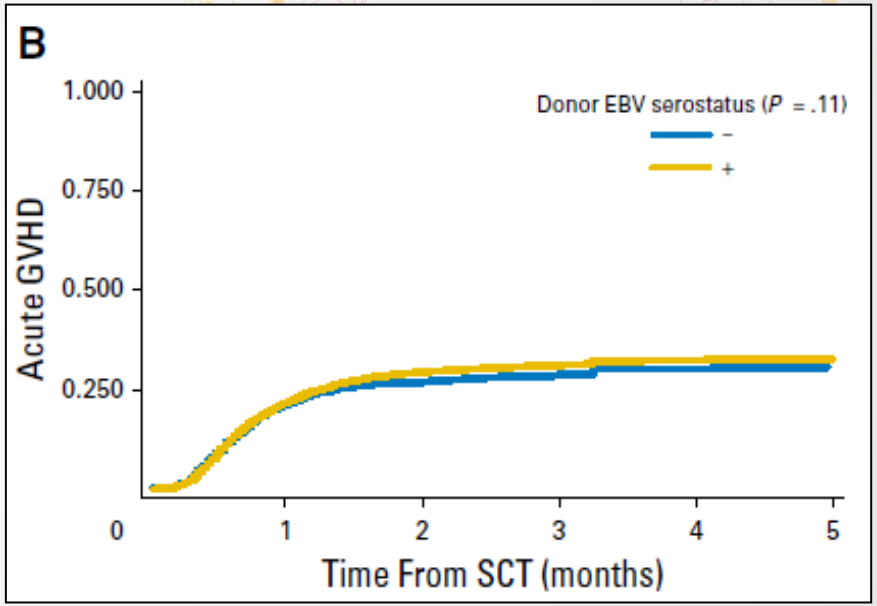






EBV serostatus – transplant outcome



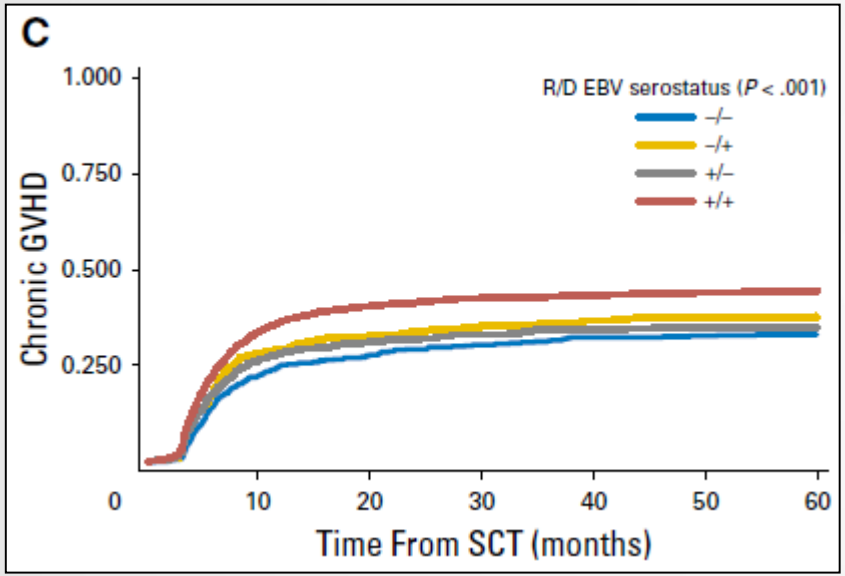


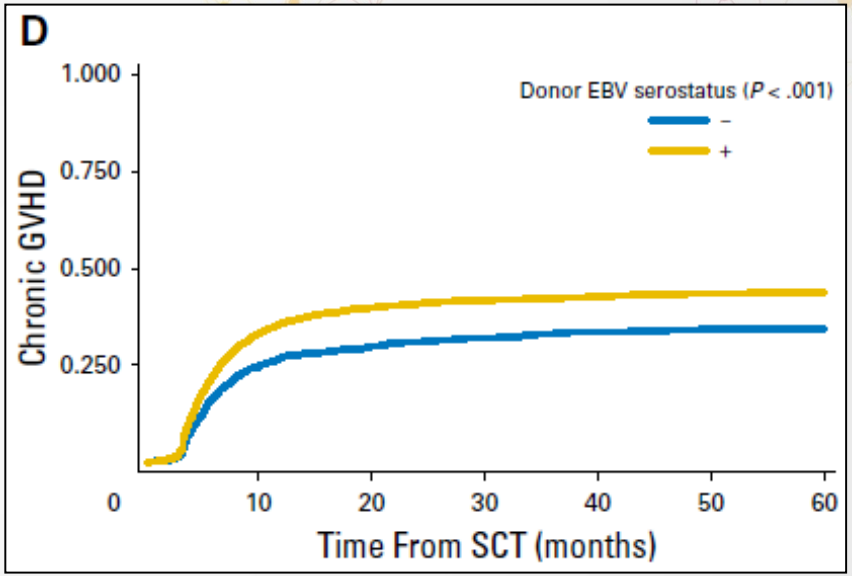
Acute GVHD

p=0.0368

p=0.1096

EBV serostatus – transplant outcome





p<0.0001

Chronic GVHD
p<0.0001

Viral infections

Important data

Serology of donor and recipient before HSCT
- CMV
- EBV

Time to reactivation

Viral load
- CMV
- EBV

Site of infection
- CMV disease

EBV-PTLD
- characteristic

Prophylaxis

Treatment
- Empirical
- Preemptive
- Targeted

Outcome

Infection - module

1A. Recipient microbiology results before HSCT

	Negative	Positive	Not done
HIV Ab	☐	☐	☐
HIV RNA	☐	☐	☐
CMV IgG	☐	☐	☐
EBV IgG	☐	☐	☐
HBsAg	☐	☐	☐
HBsAb	☐	☐	☐
HBcAb	☐	☐	☐
HBV DNA	☐	☐	☐
HCV Ab	☐	☐	☐
HCV RNA	☐	☐	☐
HEV Ab	☐	☐	☐
HEV RNA	☐	☐	☐
HTLV 1 or 2 Ab	☐	☐	☐
Toxoplasma IgG	☐	☐	☐
Mantoux/quantiferon	☐	☐	☐
Syphilis Ab (TPHA)	☐	☐	☐
VZV IgG	☐	☐	☐
Other (specify)	☐	☐	☐

Ab, antibodies; Ag, antigen.

Infection - module

1B. Donor microbiology results before HSCT

	Negative	Positive	Not done
CMV IgG	☐	☐	☐
EBV IgG	☐	☐	☐
HBsAg	☐	☐	☐
HBsAb	☐	☐	☐
HBcAb	☐	☐	☐
HBV DNA	☐	☐	☐
HCV Ab	☐	☐	☐
HCV RNA	☐	☐	☐
HEV Ab	☐	☐	☐
HEV RNA	☐	☐	☐
HTLV 1 or 2 Ab	☐	☐	☐
Toxoplasma IgG	☐	☐	☐
VZV IgG	☐	☐	☐
Other (specify)	☐	☐	☐

Ab, antibodies; Ag, antigen.

Infection - module

2. **Infections at day +100 and Annually**

INFECTION RELATED COMPLICATIONS	YES	DATE of onset	NAME OF PATHOGEN	ADD ANOTHER INFECTION#
Bacteremia (report all episodes BSI*)	☐	yyyy-mm-dd	……	☐
Invasive fungal disease, including candidemia (report all episodes)	☐	yyyy-mm-dd	…… **site of infection:** ☐ lung ☐ blood ☐ CNS ☐ Other …… ……	☐
CNS infection	☐	yyyy-mm-dd	……	☐
Pneumonia	☐	yyyy-mm-dd		☐
C. difficile infection	☐	yyyy-mm-dd	……	☐
Abdominal infection	☐	yyyy-mm-dd	…… or specify the type of clinically documented infection, e.g. typhlitis, cholecystits, gastroenteritis, etc ……	☐
Hepatitis	☐	yyyy-mm-dd	……	☐
Retinitis	☐	yyyy-mm-dd	……	☐
Cystitis	☐	yyyy-mm-dd	……	☐
Skin infection	☐	yyyy-mm-dd	……	☐
Upper respiratory tract infection	☐	yyyy-mm-dd	……	☐
CMV reactivation (DNA-emia in serum/plasma/blood)	☐	yyyy-mm-dd of the first yyyy-mm-dd of the highest value	The highest value in ☐ copies/mL ☐ IU/mL	☐
EBV reactivation (DNA-emia in serum/plasma/blood/PMN)	☐	yyyy-mm-dd	The highest value in ☐ copies/mL ☐ IU/mL	☐
HHV6 reactivation (DNA-emia in serum/plasma)	☐	yyyy-mm-dd	The highest value in ☐ copies/mL ☐ IU/mL	☐
Adenovirus reactivation (DNA-emia in serum/plasma)	☐	yyyy-mm-dd	The highest value in ☐ copies/mL ☐ IU/mL	☐
Other	☐	yyyy-mm-dd	……	☐

* - In case of the same pathogen, report episodes occuring after 14 days
BSI – list of pathogens included below
(# - Technically: to add possibility to report additional infection)

Infection - module

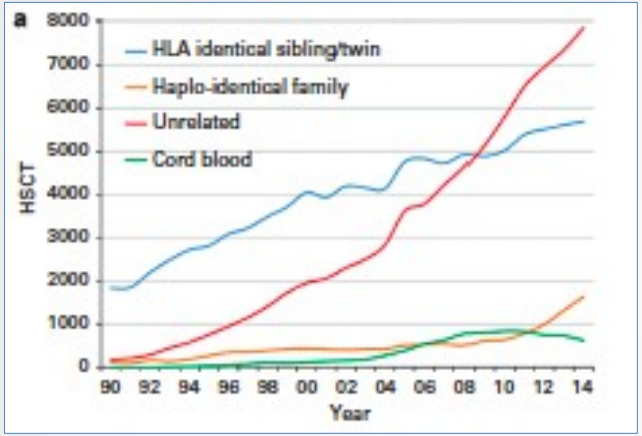
LIST OF BACTERIA FOR BLOOD-STREAM INFECTIONS (BSI)

Acinetobacter baumanii
Bacteroides fragilis
Burkholderia cepacia
Capnocytophaga (any species)
Campylobacter (any species)
Citrobacter (any species)
Corynebacterium (any species)
Enterobacter (any species)
Enterococcus (any species)
Escherichia coli
Klebsiella pneumoniae
Klebsiella other than pneumoniae
Listeria monocytogenes
Nocardia (any species)
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens
Stenotrophomonas maltophilia
Staphylococcus aureus
Staphylococcus other than *aureus (significant only if ≥2 blood cultures are positive)*
Streptococcus mitis/ milleri/viridans
Streptococcus pneumoniae
Other: ……

LIST OF FUNGI FOR BLOOD-STREAM INFECTIONS (BSI)

Candida albicans,
Candida galabrata,
Candida parapsilosis,
Candida krusei,
Candida tropicalis,
Fusarium (any species),
Cryptococcus neoformas,
Other: ……

Infections after HSCT



AlloHSCT: 1993-1997 vs 2003-2007
Patients: 1418 vs 1148

Overall mortality
Non-relapse mortality
Relapse rate or progression of malignant condition

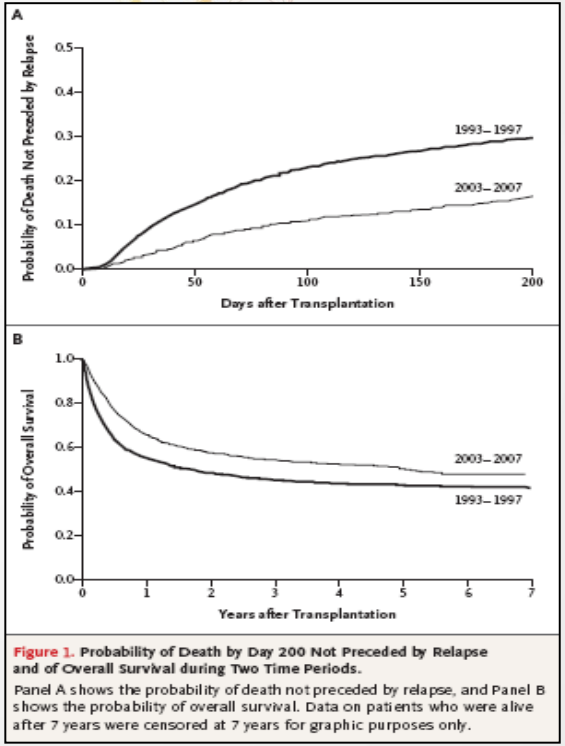


Figure 1. Probability of Death by Day 200 Not Preceded by Relapse and of Overall Survival during Two Time Periods.

Panel A shows the probability of death not preceded by relapse, and Panel B shows the probability of overall survival. Data on patients who were alive after 7 years were censored at 7 years for graphic purposes only.